Physiological and Medical Monitoring for En Route Care of Combat Casualties

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Background: **Most prehospital medical interventions during civilian and military trauma casualty transport fail to utilize advanced decision-support systems for treatment and delivery of medical interventions, particularly intravenous fluids and oxygen. Current treatment protocols are usually based on standard vital signs (eg, blood pressure, arterial oxygen saturation) which have proven to be of limited value in detecting the need to implement an intervention before cardiovascular collapse. A primary objective of the US Army combat casualty care research program is to reduce mortality and morbidity during casualty transport from the battlefield through advanced development of a semiautomated decision-support capability for closed-loop resuscitation and oxygen delivery.**

Methods: **To accomplish this goal, the Trauma Informatics Research Team at the US Army Institute of Surgical Research has developed two models for evidence-based decision support 1) a trauma patient database for capture and analysis of prehospital vital signs for identification of early, novel physiologic measurements that could improve the control of closed-loop systems in trauma patients; and, 2) a human experimental model of central hypovolemia using lower body negative pressure to improve the understanding and identification of physiologic signals for advancing closed-loop capabilities with simulated hemodynamic responses to hemorrhage.**

Results: **In the trauma patient database and lower body negative pressure studies, traditional vital sign measurements such as systolic blood pressure and oxygen saturation fail to predict mortality or indicate the need for life saving interventions or reductions in central blood volume until after the onset of cardiovascular collapse. We have evidence from preliminary analyses, however, that indicators of reduced central blood volume in the presence of stable vital signs include 1) reductions in pulse pressure; 2) changes in indices of autonomic balance derived from calculation of heart period variability (ie, linear and non-linear analyses of R-R intervals); and 3) reductions in tissue oxygenation.**

Conclusions: **We propose that derived indices based on currently available technology for continuous monitoring of specific hemodynamic, autonomic, and/or metabolic responses could provide earlier recognition of hemorrhage than current standard vital signs and allow intervention before the onset of circulatory shock. Because of this, such indices could provide improved feedback for closed-loop control of patient resuscitation and oxygen delivery. These technological advances could prove instrumental in advancing decision-support capabilities for prehospital trauma care during transport to higher levels of care in both the military and civilian environments.**

Key Words: **Closed-loop fluid resuscitation, Closed-loop oxygen delivery, Hypovolemia, Arterial blood pressure, Pulse pressure, Heart period variability.**

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Military capabilities for care of casualties during transport differ from civilian capabilities in three fundamental ways: 1) combat medical personnel who accompany the casualty during transport may not have advanced medical training compared with civilian emergency medical system medics; 2) combat flight medics must perform their role as warfighters to assure crew and aircraft safety in a hostile environment; and 3) the availability of resources such as oxygen and resuscitation fluids are restricted due to weight and space limitations in the combat environment. These three limitations could be addressed with the development of medical monitoring technology designed to provide physiologic feedback for autonomous control of the delivery of oxygen and resuscitation fluids during transport to higher levels of care. Unfortunately, currently designed closed-loop systems are controlled by standard vital signs (eg, blood pressure, arterial oxygen saturation) that can be inadequate for early detection of a need to implement an intervention.[1–3] Thus, a primary objective of the US Army combat casualty care research program is to reduce morbidity and mortality during casualty transport through development of a continuum of capabilities ranging from open-loop decision support to autonomous closed-loop resuscitation and oxygen delivery.

To accomplish this goal, the Trauma Informatics Research Team at the US Army Institute of Surgical Research is focused on the identification of new medical monitoring

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approaches that can provide evidence-based decision support capabilities for closed-loop care during casualty transport from the point of injury (prehospital) through higher levels of care (eg, combat support hospital, intensive care unit). The purpose of this paper is to provide a review of published and preliminary findings obtained from our research program that support the ultimate goal of reducing morbidity and mortality during casualty transport.

MATERIALS AND METHODS

Prehospital Data Warehousing System

We developed a data warehousing system for the capture and analysis of civilian prehospital patient vital signs to develop advanced on-the-scene and en route decision support for medical personnel. This system permits warehousing of patient information, and treatments and outcomes for use in the verification and validation of trauma injury models. The system has the capability to automatically record real-time numeric and wave form data from severely injured trauma patients during the prehospital transport phase. In the patient records, prehospital physiologic data are merged with prehospital and hospital interventions, resulting in a complete representation of physiologic status in addition to treatments and patient outcome. Researchers can query the system for particular data sets that can be exported for additional analysis.

The trauma vitals system is currently operating in the Memorial Hermann Life Flight service in Houston, TX, and the Air Life service in San Antonio, TX. Helicopters are equipped to record trauma patient data from transports in the metropolitan and surrounding areas to the Level I trauma centers at the Memorial Hermann Hospital in Houston, and Brooke Army Medical Center and the University of Texas Health Science Center in San Antonio. Research nurses manage collection and uploading of patient data to the database. The current system contains over 2900 fully correlated incident records with prehospital, hospital, and outcome data. Data from all recorded incidents are stored and correlated using a relational database engine that provides the data management tools for storage and warehousing of records, in addition to providing the querying engine for data analysis and algorithm testing. The database system has been recently expanded to include collection of trauma vital signs from the Combat Support Hospital in Baghdad, Iraq.

The initial data recording system included the capture of data from multiple simultaneous sources and a personal digital assistant (PDA) attached to a Propaq model 206EL vital signs monitor. The collected data were stored on a removable card loaded onto the PDA. The initial Propaq/PDA data recording system has been replaced by a Welch Allyn PIC 50 vital signs monitor that provides more stable electrocardiograph (ECG) waveforms and improved patient data recording on a built-in PCMCIA linear flash card. Using an applet-based approach, the stored image from the PIC 50 monitor can be easily uploaded and converted into the internal format of the trauma vitals system.

To create a complete record of a trauma patient, data are collected from all critical care treatment phases, from scene of injury and transport to the ED to final patient outcome. Specific data include: 1) estimated time of incident and additional event times as an offset of the time of incident without dates, names, or other identifying information in accordance with the Health Insurance Portability and Accountability Act (HIPAA); 2) manual recordings of patient injuries and method of injury provided by the paramedics; 3) manual pulse character obtained from the radial, femoral, and carotid arteries; 4) Glasgow Coma Score (GCS) at the incident scene; 5) manual respiration rates and blood pressures recorded directly by emergency personnel; 6) manual entries of all interventions performed by prehospital emergency medical personnel; 7) automatic numeric and wave form vital signs; 8) fluid types and volume given en route, in the ED, and during the first 24 hours; 9) hospital data recorded by medical personnel; 10) all interventions performed in the ED or operating room; 11) International Classification of Diseases (ICD-9) for all diagnosis and interventions performed in the ED; 12) other data including fluids and other interventions given after the first day of treatment; and, 13) patient outcome (mortality).

A client/server system is used to correlate and manage both automatic and manually collected data sets. Once a patient record has been loaded and verified by the system data managers, the record becomes part of the data warehouse and is available for queries by system users. These queries can be performed through the use of selection (drop-down menus) and range operators that allow researchers to access every data item on the incident record. For example, if an operator wanted to evaluate intubated patients, the intubation intervention can be selected from a pull-down menu and added to the query. If a single item is added to the list, all records that contain the item will be retrieved in a query. Range operators are used for selection of data items that have numeric ranges. Multiple selections within a particular data item, such as the presence of life saving intervention (LSI; Table 1), are chained as 'OR' queries, whereas multiple selections across

Table 1 List of 12 Categories of Pre- or In-hospital LSIs

Blood transfusion
Cardioversion
Chest tube
Cardiopulmonary resuscitation
Intubation
Pericardiocentesis
Cricothyrotomy
Thorocotomy
Angiography with embolization
Angiography without embolization
Needle decompression
Surgical intervention

different data items, such as prehospital LSI and prehospital noninvasive blood pressures, are treated as 'AND' queries. Items stored as free text (such as descriptions) can be queried using an "*" operator for matching one or more text patterns in the field. Query results are returned to the user as a list of patient records that match the various query inputs. Query results can be further limited by selecting/unselecting individual patient records from the results page. The remaining selected records can be exported to the local user's computer for further analysis and validation. In cases of large file sizes, the user has the option to select captured data streams that can be exported to a local machine with the rest of the records. This format is useful for exchanging data files between systems by creating a self-describing file format that can easily be exchanged across heterogeneous systems. A character delimited file export can generate the selected records as a text file that can be imported into commercially available data software.

Human Laboratory Model of Central Hypovolemia

Although critical to providing guidance for future research and development of advanced decision-support for the control of closed-loop systems, the trauma vitals data warehousing system has several important limitations. First, the significantly large variability that is inherent to field data collection on real-world trauma patients (eg, dirty signals, missing data, differences in injury modality and severity) requires large sample sizes for valid statistical analysis and interpretation of data. Second, the ability to obtain important trending data on physiologic measurements could provide insight for early assessment of patient status or outcome, but as in any clinical study, it is difficult to interpret these data in the absence of complete information on the preinjury physiology or postinjury time(s) when clinical interventions were applied. Finally, most trauma patient databases contain an array of vital signs obtained from standard medical monitoring devices and physical examination of the patient. The fundamental assumption is that these traditionally accepted clinical measures of hypotension and other signs and symptoms of hemorrhagic shock mark the beginning of circulatory compromise rather than the beginning of decompensation. Historically, laboratory animal models of hemorrhage have been used to address some of these limitations, but the potential impact of anesthesia on compensatory mechanisms and the absence of mental status assessment can limit the clinical correlates to human trauma patients. Development of effective indicators that predict the magnitude and/or rate of progressive hemorrhage before the onset of hemorrhagic shock (i.e. pre-shock phase of hemorrhage) must necessarily be based on carefully controlled human experimentation. However, controlled study of severe hemorrhage in humans is not possible. Thus, a model that simulates central blood loss in humans would be most attractive to extend and verify the utility of continuous recordings of both standard and novel vital signs that cannot be easily obtained from trauma patients due to the extreme difficulties associated with clinical assessments in austere environments.

Lower body negative pressure (LBNP) has been used in our research program as an experimental tool to simulate loss of central blood volume (eg, hemorrhage) in humans.[4] With the use of a neoprene skirt designed to form an airtight seal between the subject and the chamber, the application of negative pressure to the lower body (below the iliac crest) results in a redistribution of blood away from the upper body (head and heart) to the lower extremities and abdomen (Fig. 1A). Thus, this model provides a unique method of investigating physiologic signals under conditions of controlled, experimentally-induced hypovolemic hypotension in otherwise healthy humans. Absolute equivalence between the magnitude of negative pressure applied and the magnitude of actual blood loss cannot at this time be determined, but review of both human and animal data reveal ranges of effective blood loss caused by LBNP. On the basis of the magnitude of central hypovolemia, we have previously proposed that 10 to 20 mm Hg negative pressure induces hemodynamic responses that are equivalent to those resulting from blood loss ranging from 400 to 550 mL; 20 to 40 mm Hg

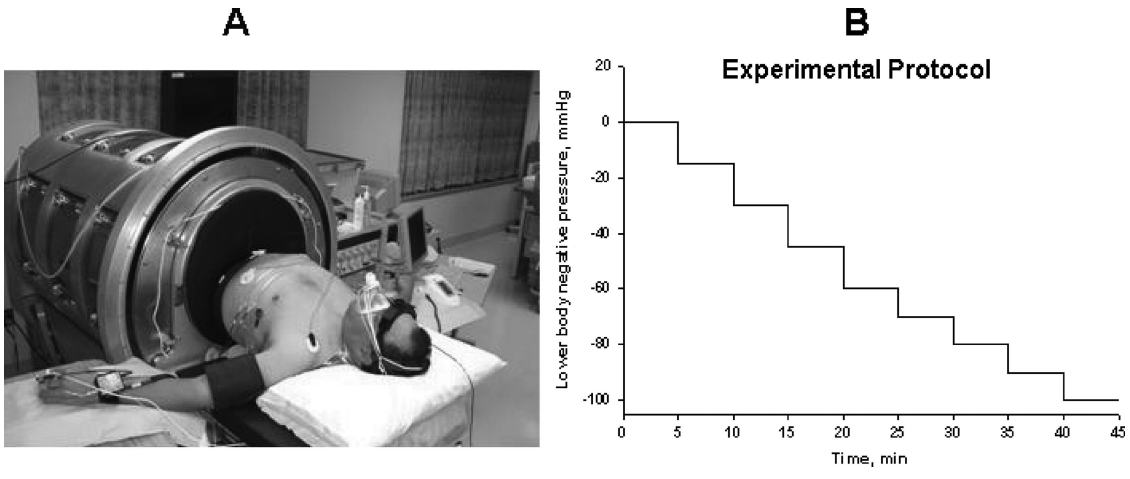

Fig. 1. *Subject in the LBNP device* (A) *and the LBNP protocol* (B).

negative pressure induces hemodynamic responses that are equivalent to those resulting from blood loss ranging from 550 to 1,000 mL; and greater than 40 mm Hg negative pressure induces hemodynamic responses that are equivalent to those resulting from blood loss approximating 1,000 mL or more. Thorough reviews of such comparisons can be found in our previous work.[4,5] As depicted in Figure 2, continuous bleeding in anesthetized pigs (left panels) and progressive LBNP in humans (right panels) elicits similar reductions of cardiac output and compensatory increases of heart rate. We use a progressive LBNP protocol designed to experimentally-induce hypotensive hypovolemia until the onset of cardiovascular collapse (Fig. 1B). Cardiovascular collapse is defined by one or a combination of the following criteria: 1) a precipitous fall in systolic blood pressure (SBP) greater than 15 mm Hg; 2) a sudden decrease in heart rate (HR) >15 bpm; 3) progressive diminution of SBP below 70 mm Hg; and/or 4) voluntary subject termination due to onset of presyncopal symptoms such as gray-out, sweating, nausea, or dizziness.

A significant limitation of LBNP is that we cannot reproduce, and consequently study, the physiology of hemorrhagic shock in humans because hypotension is not sustained and does not result in end organ failure or metabolic acidosis. Our emphasis, therefore, is placed on understanding the physiology of progressive central hypovolemia that leads to cardiovascular decompensation and may represent the precursor to hemorrhagic shock (ie, during the preshock phase of hemorrhage), a time when intervention(s) could prove more effective than after the onset of cardiovascular decompensation. Thus, the strength of the LBNP model is that it provides a capability to identify physiologic measures that are altered in advance of standard vital signs and well before the onset of cardiovascular collapse. Therefore, the primary objectives of the LBNP model of hypovolemia are to: 1) correlate observations reported from vital sign analyses of trauma patients with hemorrhagic injury with those of controlled central hypovolemia in the laboratory setting; and, 2) obtain new insight for the development of decision-support algorithms based on novel physiologic measurements other than standard vital signs. We will use this review to report and compare beat-by-beat estimates of arterial pressures (infrared finger photoplethysmography), R-to-R intervals (RRI), HR (electrocardiogram), pulse pressure [SBP − diastolic blood pressure (DBP)], stroke volume (SV; thoracic electrical bioimpedance and infrared finger photoplethysmography), cardiac output (CO = HR × SV), total peripheral vascular resistance [mean arterial pressure (MAP)/CO], muscle sympathetic nerve activity (microneurography), blood lactate, blood base deficit, arterial oxygen saturation (SpO_2; pulse oximetry), and tissue (muscle) PO_2 and pH (near-infrared spectroscopy) in conscious human subjects exposed to progressive central hypovolemia using LBNP with standard vital sign measurements of HR, blood pressures (auscultation), shock index (HR/SBP), and SpO_2 recorded in trauma patients to identify potential earlier indicators of the need for oxygen delivery or fluid resuscitation during casualty transport and in-hospital care.

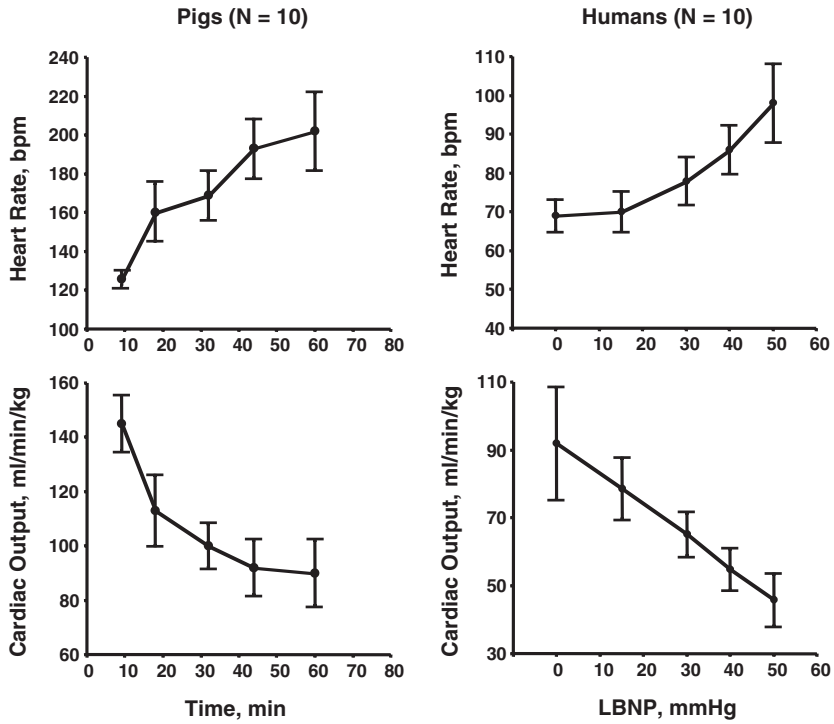

Fig. 2. *Comparison of elevated heart rate and reduced cardiac output during 65 minutes of hemorrhage in ten pigs (left panels) and graded LBNP in 10 human subjects (right panels). Circles and lines represent mean ± SE values. Figure reproduced from Cooke et al.*[4]

RESULTS

Utility of Standard Vital Signs for Monitoring Fluid Resuscitation Requirements

Automated Monitoring of Standard Vital Signs. Current medical monitors used in emergency vehicles, EDs, and ICUs provide measurements of SBP, DBP, MAP, SpO_2, end-tidal CO_2, HR, and respiration rate. Using the trauma patient database, a preliminary analysis of 216 patients was conducted to determine the association between standard vital signs and patient outcome. Using a multivariate logistic regression analysis, SBP <90 mm Hg and Glasgow Coma Scale motor function score (GCSm) <6 predicted the need for an LSI.[6] However, 21% of patients with "normal vital signs" still required an LSI. The analyses of these preliminary data clearly emphasized that once cardiovascular collapse and circulatory shock occur, standard vital signs become abnormal and indicative of outcome. It is, therefore, not surprising that currently designed closed-loop devices for fluid resuscitation are controlled by measurement of blood pressure. Although SBP may provide a feedback signal once it is abnormal, it may not be the most sensitive feedback signal for determining adequacy of resuscitation when compensatory physiologic mechanisms are acting to maintain SBP in the presence of reduced circulatory blood volume or tissue hypoperfusion.

Manual Examination versus Automated Monitoring. Pulse character, classified as normal or abnormal (weak or absent), was analyzed from the medical records of 342 patients obtained from our trauma vital signs database.[7] An abnormal radial pulse character was associated with significantly lower SBP (average of 102 mm Hg) compared with patients with a normal pulse (associated with an average SBP of 128 mm Hg), and a rise in patient mortality was associated with worsening pulse character. These data suggest that an abnormal (weak or absent) radial pulse may be an acceptable method for initial rapid triage and evaluation for the titration of fluid resuscitation in trauma patients and provide evidence for pulse evaluation to be included as part of the Tactical Combat Casualty Care triage algorithm for battlefield casualties.[8,9]

As an extension to the simple application of radial pulse character evaluation, we determined if increasing the complexity of current automated medical monitors might improve their power to determine the need for an LSI. We calculated and compared the receiver operator characteristic (ROC) curve areas obtained from diagnostic equipment to vital signs and motor scores obtained only by physical examination on 381 prehospital trauma patient records collected during helicopter transport by emergency medical system personnel.[10] Clinical assessments of these patients were categorized into three sets by selective inclusion of physical examination and vital signs data: Set 1 (physical examination only) had vital signs obtained with no equipment (radial, femoral, and carotid pulse character; capillary refill; motor and verbal components of the GCS); Set 2 (physical examination with simple automation) included Set 1 plus eye component of the GCS and pulse oximetry for SpO_2; and Set 3 (fully automated) included Set 2 plus fully automated noninvasive blood pressure measurements, HR, end-tidal CO_2, and respiratory rate. LSIs performed during transport and in the hospital were recorded. Radial pulse character and GCS verbal and motor components were most strongly associated with the need of a prehospital LSI in Set 1 (ROC curve area = 0.97). Radial pulse character together with the eye and motor component of the GCS provided the best relationship of a need for a prehospital LSI for Set 2 (ROC curve area = 0.97). Addition of all supplementary vital signs measured by an automated monitor (Set 3) resulted in a ROC curve area of 0.97. Thus, the need for an LSI can be indicated equally well from simple measurements obtained from physical examination as those recorded from current automated medical instrumentation that provide standard vital signs.

The shock index (SI), which is the ratio between HR and SBP, has been reported to be a sensitive marker of hypovolemia and shock.[11,12] However, analyses performed on vital signs obtained from our database revealed that the SI of trauma patients who present with normal vital signs but require an LSI was not statistically different from the SI of patients who did not receive an LSI (Fig. 3). The importance of these findings is that they reinforce the notion that standard vital signs based on changes in blood pressure and heart rate may add little to decision support to identify the need for an LSI or fluid resuscitation when they are within normal clinical values.

Late Versus Early Detection of the Need for Fluid Resuscitation. A limitation of using standard vital signs for determining the need for fluid resuscitation is the existence of a subset of trauma patients whose compensatory physiologic mechanisms prevent these signs from changing early, thus potentially delaying fluid intervention and increasing the risk of poor outcome. The reporting by military surgeons and medics of combat casualties who enter a Combat Support

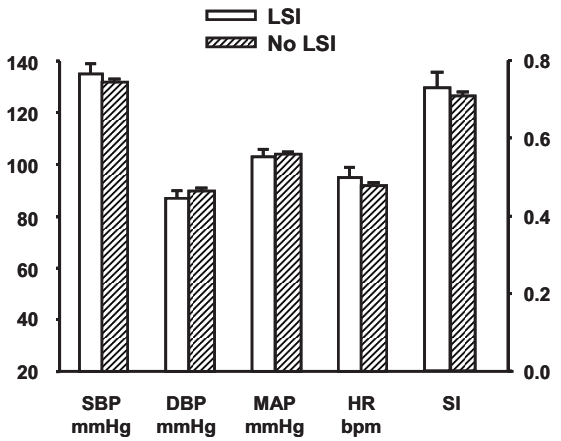

Fig. 3. *SBP, DBP, MAP, HR, and SI are shown for 46 trauma patients who received an LSI and 200 trauma patients who did not receive an LSI. Bars and lines represent mean ± SE values.*

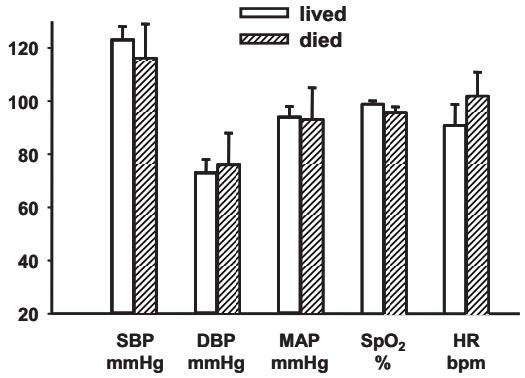

Fig. 4. *SBP, DBP, MAP, SpO_2, and HR are shown for 15 patients who died and 15 patients who survived traumatic injuries requiring transport to a level one trauma center. Bars and lines represent mean ± SE values. Data modified from Cooke et al.[1]*

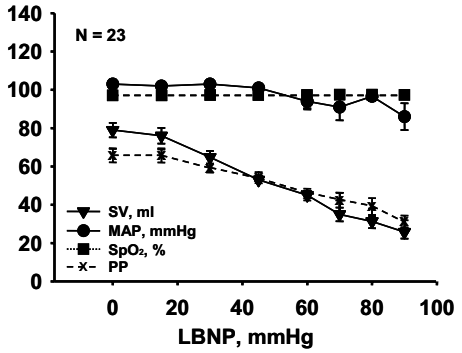

Fig. 5. *Responses of MAP (circles, solid line), SpO_2 (squares, broken line), SV (inverted triangles, solid line), and PP (crosses, broken line) to progressive central hypovolemia induced by LBNP. Symbols and lines represent mean ± SE values. Data were extracted from Convertino et al.[23]*

Hospital with normal vital signs but thereafter decompensate best supports this notion.

We recently examined the ability to obtain an early indication of patient outcome based on measurements of standard vital signs.[1] We compared a group of trauma patients with severe hemorrhage who lived with a group matched for age and gender who did not live. All patients suffered from blunt or penetrating injuries without significant head injury, thus focusing our analysis on patient outcome due to hemorrhage (ie, a need for fluid resuscitation). Vital signs were collected between 42 and 87 minutes following injury, and the median time to death was 9.5 hours. Our results demonstrated that there were no statistical differences in standard vital signs obtained from a standard monitor at the scene of injury between patients who survived and those who died (Fig. 4). These data from severely hypovolemic trauma patients support previous observations that standard vital sign measurements can fail to provide specific indications of severity of blood loss and impending fluid resuscitation requirements before cardiovascular decompensation.[13] These patient data are supported by laboratory experiments that demonstarted that SBP, SpO2, end-tidal CO_2, pulse character, and onset of symptoms (e.g., GCSm) do not always provide early indication of reductions in central blood volume until just before cardiovascular collapse.[4,14–20] Thus, it might be inferred that a limitation to the use of standard medical monitors for feedback decision support for fluid resuscitation by medical personnel or autonomous closed-loop devices is the inability to provide measurements well before the onset of cardiovascular collapse and decompensation.

Utility of Standard Vital Signs for Monitoring Tissue Oxygen Requirements

Oxygen Saturation. Because of the simplicity, ease, and availability of the pulse oximeter, it is not surprising that currently designed closed-loop devices for oxygen delivery are controlled by measurement of SpO_2.[21] Measurement of SpO_2 has also been used ubiquitously to monitor all trauma patients without data supporting the ability of this parameter to track tissue dysoxia. Our analysis of automated monitoring of vital signs obtained from trauma patients who sustained blunt or penetrating injuries leading to hemorrhage included SpO_2 measured with a finger pulse oximeter. The results indicate that there was no statistical difference in SpO_2 in patients who lived and those who died (Fig. 4). Subsequently, we analyzed pulse oximeter measurements obtained from 23 human subjects exposed to progressive central hypovolemia induced by the application of LBNP (Fig. 5). Consistent with the trauma patient data, MAP (circles) and SpO_2 (squares) were unaltered during progressive LBNP despite >50% reductions in SV (inverted triangles). From these data, it is clear that SpO_2, in the absence of airway difficulties, does not provide information as to the level of central hypovolemia in trauma patients. It is possible, however, that changes in the SpO_2 wave form (e.g., height, width, or area under the curve) might form the basis of a future monitoring system designed to determine the severity of tissue dysoxia associated with central hypovolemia. This possibility is currently under investigation in our laboratory.

Summary of Standard Vital Signs for Closed-Loop Resuscitation and Oxygen

Because a major limitation of current vital sign monitors is their collection of physiologic measurements (ie, blood pressure, SpO_2) that may not change until the patient decompensates, it may not be unexpected that manual examination in our patient population resulted in a similar association with LSIs compared with the use of monitors. Recent work at the US Army Institute of Surgical Research indicates that new monitoring approaches and technologies that provide capabilities for continuous trend analysis, in addition to alternative measures of compensatory responses to blood loss, may allow the healthcare provider earlier indicators for the titration of fluid resuscitation or oxygen delivery than either

physical examination or static automated measures of outcome vital signs. Automated vital sign monitors can provide a decision-support advantage to medical personnel for autonomous closed-loop fluid resuscitation and oxygen delivery provided that the most sensitive indices for early detection of impending cardiovascular collapse are identified and displayed during the preshock stage of care. The ability of "new" vital signs to accurately monitor the appropriate level of resuscitation will require their application in clinical testing such as that currently being conducted in trauma care.[21,22]

Alternative Measurements for Monitoring Fluid Resuscitation Requirements

Pulse Pressure. It is clear from Figure 5 that continuous measurement of SV represents one of the most sensitive and specific measures of early reductions in central blood volume when blood pressures and SpO_2 have not yet changed. Thus, any physiologic response that tracks alterations in SV should provide an effective indicator for early detection of blood loss and the need for fluid resuscitation. Analysis of vital sign data collected from trauma patients who sustained blunt or penetrating injuries leading to severe hemorrhage revealed that patients who died had statistically lower pulse pressures (PP) at the time of emergency medical personnel arrival than those who lived, even when there were no differences in SBP, HR, or SpO_2.[1] When we performed continuous measurements of PP with SV, blood pressure and SpO_2 in human volunteers who underwent progressive central hypovolemia induced by LBNP,[23] PP proved to be a significantly earlier indicator of central blood volume reduction than MAP or SpO_2 because of its ability to track SV (Figs. 5 and 6). Thus, both trauma patients and laboratory experimental data obtained from hypovolemic humans suggest that a reduction in PP may provide an indicator of fluid resuscitation requirements before blood pressure begins to decrease. This approach is particularly attractive since PP can be easily calculated from measurements available on current monitors (SBP − DBP). However, the use of PP as part of an algorithm for the prehospital triage of battlefield casualties or closed-loop resuscitation is limited to the presence of monitors with capabilities to measure blood pressure.

Electrocardiogram Waveforms. Previous animal and human experiments have suggested that a reduction in central blood volume can alter the amplitude of R-waves in various ECG leads depending on underlying pathophysiology.[24–27] Using our LBNP model to reduce central blood volume, we were able to record "clean" lead II ECG waveforms and make simultaneous measurements of HR, estimated SV, SBP, DBP, and MAP during baseline supine rest, and progressive central blood volume loss in healthy human volunteer subjects.[16] LBNP resulted in a significant progressive reduction in central blood volume as indicated by a maximal decrease of 65% in SV and maximal elevation of 56% in HR from baseline to −60 mm Hg LBNP. R-wave amplitude increased ($p < 0.0001$) linearly with progressive LBNP. The amalgamated correlation (R^2) between average SV and average R-wave amplitude at each LBNP stage was 0.989 (Fig. 7). Our results indicate that changes of R-wave amplitudes occur before changes of arterial blood pressures, and, therefore amplitude monitoring may allow for early detection for the need of fluid resuscitation. However, the usefulness of R-wave amplitude as an indication of blood loss and subsequent fluid resuscitation may be compromised because of an array of conditions that may influence the ECG wave form (e.g., edema, body position, and signal noise).

Linear and Nonlinear Metrics of Heart Period Variability. Using our LBNP model, we demonstrated a linear relationship between changes in central blood volume and responses of sympathetic nerve activity (Fig. 8).[28] This relationship indicated that any index of sympathetic nerve activity could act as an effective marker for early detection of reduced blood volume and the need for fluid resuscitation. Although direct measurements of sympathetic nerve activity are not practical in trauma patients, metrics of the variability in the heart period obtained from an ECG have been reported to reflect autonomic (sympa-

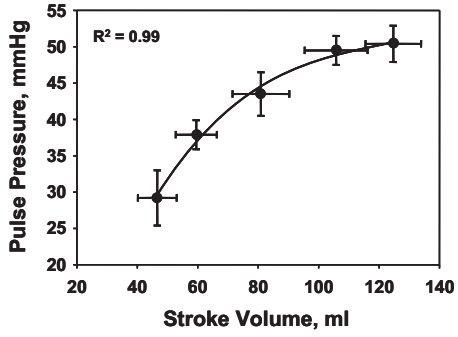

Fig. 6. *The second-order relationship and amalgamated correlation (R^2) between average SV and average PP at each LBNP stage obtained from 13 human volunteers. Circles and lines represent mean ± SE values. Figure reproduced from Convertino et al.[23]*

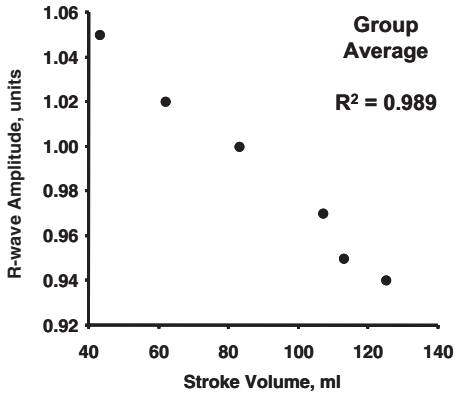

Fig. 7. *The linear relationship and amalgamated correlation (R^2) between average SV and average R-wave amplitude at each LBNP stage obtained from 13 human volunteers. Figure reproduced from McManus et al.[16]*

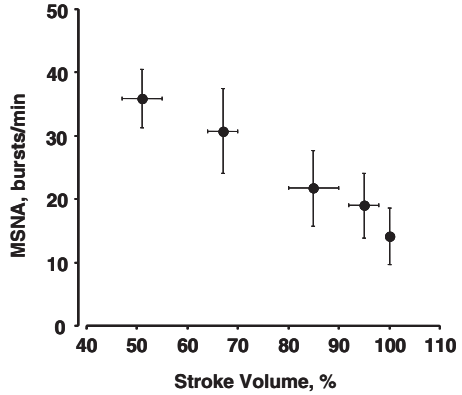

Fig. 8. *Linear relationship between relative change (%Δ) in SV and MSNA during progressive central hypovolemia. Circles and lines are means ± SE (*N = 6*). Figure reproduced from Convertino et al.*[28]

thetic and vagal) activities. For instance, the standard deviation (SD) of the RRI (RRISD) can be used as an index of cardiac vagal tone.[29] Similarly, the high-frequency (HF) power spectra generated from application of fast Fourier transform on RRI can provide a noninvasive assessment of parasympathetic nervous activity.[30] Using our LBNP model, we recently demonstrated strong correlations among increases of sympathetic nerve activity and decreases of RRISD (R^2 = 0.96) and HF (R^2 = 0.98) during progressive reductions in central blood volume in humans.[31] That is, sympathetic activation and parasympathetic withdrawal are associated with compensatory responses to hypovolemia, and the latter may be tracked noninvasively. Nonlinear complexity calculations represent another analytical tool for assessment of autonomic responses since such metrics represent a potential indicator of the presence of hypovolemia in animal hemorrhage studies.[32,33] Subsequent analyses of our human subjects who underwent progressive reduction in central blood volume in LBNP revealed that RRISD, HF, and various nonlinear complexity metrics all provide early indication of central hypovolemia when standard vital signs are not changing (Fig. 9).

RRI data obtained from trauma patients also provide insight into the potential use of heart period variability as an assessment tool for the feedback control of fluid resuscitation. Analysis of data from our trauma patient database revealed that patients who lived had statistically lower HF power than those who died (Fig. 10),[1,2] suggesting appropriate autonomic compensation that was associated with survival. The analyses in these trauma patients are consistent with our experimental results obtained from humans undergoing LBNP, in that reductions in heart period variability reflect adequate autonomic compensation to progressive reduction in central blood volume before cardiovascular decompensation occurs (Fig. 9). Further analyses demonstrated that loss of RRI complexity is also associated with outcomes in trauma patients.[34] The calculation of some index associated with RRI variability to assess blood volume status of

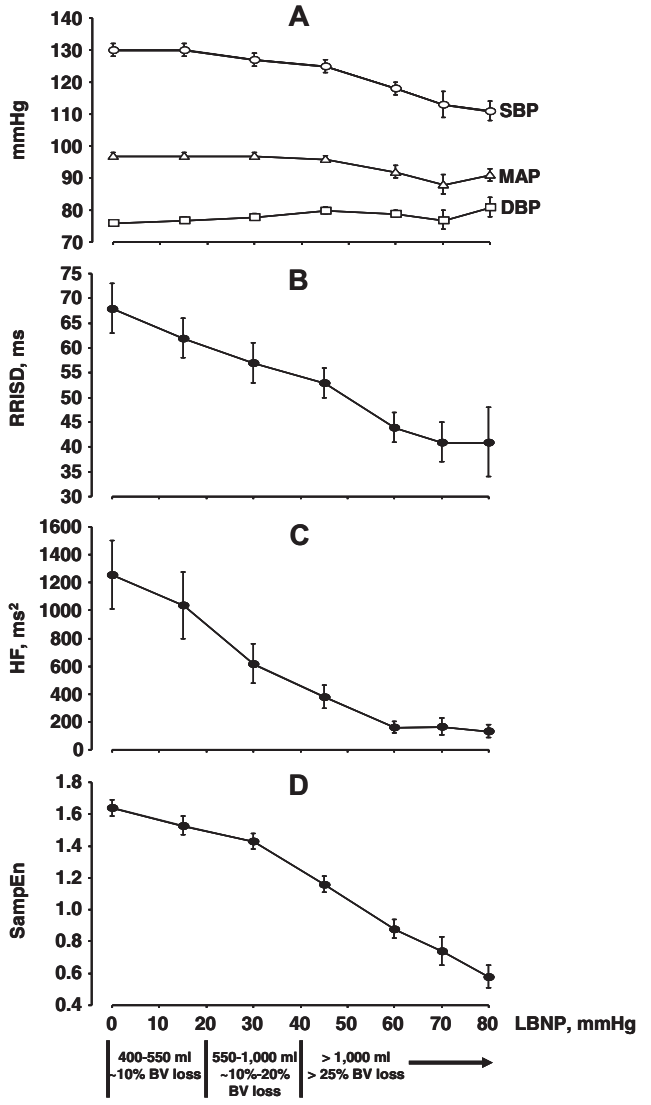

Fig. 9. *Responses to progressive central hypovolemia induced by LBNP.* A*, responses of SBP (open circles), DBP (open squares), and MAP (open triangles).* B*, SD of the RRI (RRISD).* C*, HF.* D*, Sample entropy (SampEn). Values are mean ± SE;* N = *33. Data were extracted from Cooke et al.*[31]

combat casualties is attractive since these metrics can be easily obtained and may in the future be calculated in real time from an ECG that is available on current monitors. The possibility that changes in heart period variability and PP together (e.g., ΔHF/ΔPP or some other combination) may provide a more sensitive marker of changes in blood volume awaits further investigation. These relationships suggest that linear and/or nonlinear analyses of RRI could play an important role in providing early detection of a requirement for fluid resuscitation and, therefore, a potential component of an algorithm for closed-loop resuscitation.

Spontaneous Cardiac Baroreflex Response. The cardiac baroreflex sensitivity (BRS) reflects vagal reflex responses and can be assessed by calculating the ratio of the change in

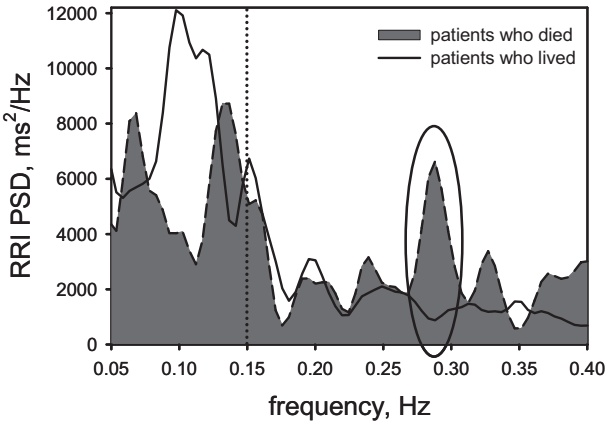

Fig. 10. *Average R-R interval power spectral density (RRI PSD) is shown for 15 patients who lived (solid line) and 15 patients who died (shaded area) from traumatic injuries requiring transport to a level one trauma center; vertical dotted line denotes the demarcation of low frequency (0.05 to 0.15 Hz) and high frequency (0.15 to 0.4 Hz) spectral bands. Ellipse represents RRI PSD at the respiratory frequency. Figure reproduced from Cooke et al.*[1]

RRI to the change in arterial pressure (e.g. ΔHR/ΔMAP). Using our LBNP model, we conducted studies to understand how cardiac BRS may be altered as a function of progressive central hypovolemia.[17] Our results demonstrate that BRS is altered as a linear inverse function of reduced central blood volume and provides earlier indication of the need for fluid resuscitation than arterial blood pressure, which remained constant. Accurate BRS measurement was independent of breathing rate and, therefore, shows promise as a tool to assist in the assessment of changing blood volume status. As this method of calculating BRS assesses the changes in both RRI and SBP, it would be necessary to temporally track these parameters. However, this calculation could be easily achieved with the currently available measures of HR and arterial blood pressure on traditional monitors. It is, therefore, possible that changes in autonomic vagal activity reflected by altered BRS could serve as an important adjunct to monitoring of HR, heart period variability and arterial pressures, track progression to hemodynamic instability in bleeding patients, and assist in the early assessment for control of closed-loop resuscitation.

Arterial Blood Pressure Oscillations. Mean arterial blood pressure is maintained during significant reduction in central blood volume by compensatory reflex mechanisms (Fig. 5), making it difficult to determine the requirement for resuscitation fluids following hemorrhage. However, central hypovolemia causes increases in arterial pressure oscillations that cannot be measured with the use of standard medical monitors that require a minimum of 30 seconds to detect systolic and diastolic Korotkoff sounds. This is best illustrated in Figure 11, where beat-to-beat blood pressure tracings were recorded in one of our human subjects over a period of 60 seconds at baseline rest and 100 mm Hg LBNP (estimated >1000 mL reduction in central blood volume) using infrared photoplethysmography on a finger. When blood pressure was measured with a standard blood pressure auscultatory cuff, arterial pressures were similar at both rest and LBNP with SBP ~115 mm Hg and DBP ~75 mm Hg. Despite quite different beat-to-beat BP responses, Figure 11 illustrates that systolic and diastolic Korotkoff sounds measured at times "a" and "b" over a 30-second time interval can result in similar blood pressures (indicated by the intercept of the horizontal broken lines on the BP axis). However, it is clear from the tracings in Figure 11 that pulse pressure is significantly reduced at 100 mm Hg LBNP with blood pressures that oscillate between 110/90 and 90/70. These preliminary experiments indicate that arterial pressure oscillations increase proportionately to progressive reduction in central blood volume and, therefore, change at an earlier time than average

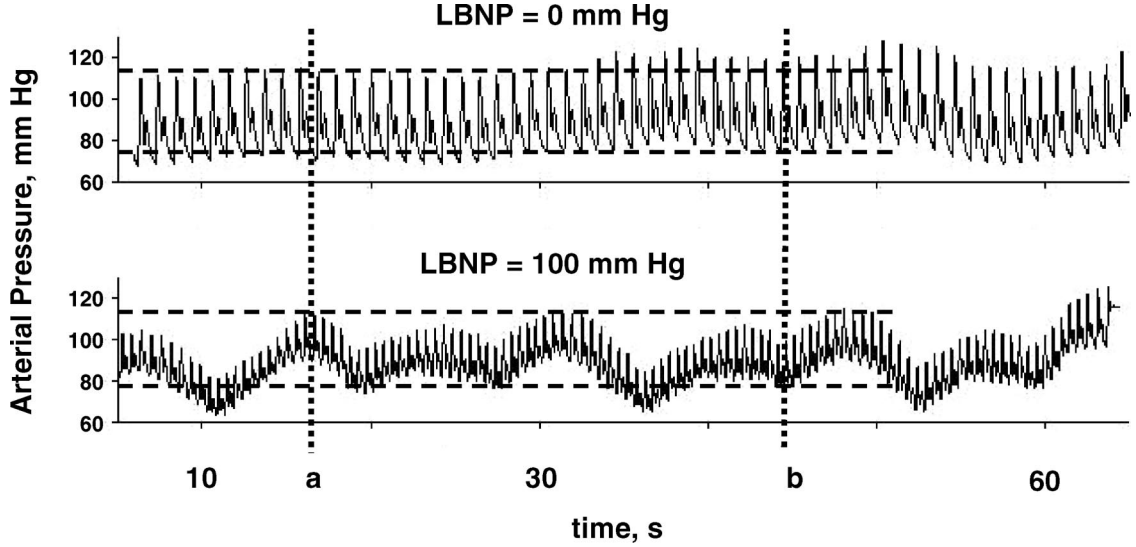

Fig. 11. *Beat-to-beat arterial blood pressure tracings at baseline rest (upper tracing) and 100 mm Hg LBNP (lower tracing).*

SBP. These results suggest that measurement of arterial pressure oscillations with infrared photoplethysmography technology could provide an earlier control input for closed-loop fluid resuscitation than that currently obtained from standard blood pressure measurements.

Alternative Measurements for Monitoring Tissue Oxygen

Muscle Tissue Oxygenation. Early recognition of the need for oxygen under conditions of tissue hypoperfusion is widely believed to improve outcome and decrease the progression to multisystem organ failure by virtue of maintaining end-organ perfusion. Although blood pH and base deficit can change in trauma patients in the presence of normal blood pressure,[35] these measurements require invasive blood sampling or can be difficult to obtain in the prehospital environment and intermittently in the emergency department. These limitations result in intermittent monitoring and, consequently, will limit their usefulness for precise and continuous closed-loop feedback control. To overcome this challenge, new research is focused on the development of novel technologies [such as near-infrared spectroscopy (NIRS)] designed to continuously and noninvasively measure markers of early tissue hypoperfusion.[36]

Since muscle oxygen tension (PmO_2) decreases during tissue hypoperfusion before changes in blood pH,[37] we used our LBNP model to test the hypothesis that PmO_2 would provide an early indication of the need for oxygen. Although a variety of NIRS devices are available,[36] we used one that isolates the measurement of oxygen in muscle from that in skin and subcutaneous tissue layers.[38,39]We measured PmO_2 and muscle oxygen saturation and compared these responses to standard hemodynamic parameters and SpO_2 in ten healthy human volunteers who were exposed to progressive central hypovolemia.[40] Figure 12 illustrates the response of PmO_2, SpO_2, and SBP during progressive LBNP in one subject. Consistent with this response, all subjects demonstrated a decline in PmO_2 that paralleled the progressive reduction in central blood volume, while SBP and SpO_2 were unchanged until the time of cardiovascular collapse when SBP decreased precipitously.[40] PmO_2 was also inversely correlated with total peripheral resistance, suggesting that PmO_2 is an early indicator of a reduction in oxygen delivery through vasoconstriction. Muscle pH decreased later (Fig. 13), demonstrating the same exponential relationship with PmO_2 previously observed in animal models of hemorrhagic shock.[37] In a subsequent investigation, we found that blood pH and base deficit were not altered during the early phases of LBNP when PmO_2 was decreasing (Fig. 14). These results suggest that selective measurement of PmO_2 with NIRS technology could provide an earlier control input for closed-loop oxygen delivery than muscle oxygen saturation measured by NIRS[39] or SpO_2 currently obtained from pulse oximetry. The effective use of PmO_2 to monitor the appropriate level of oxygen delivery will require clinical testing such as that currently being conducted in trauma care.[21]

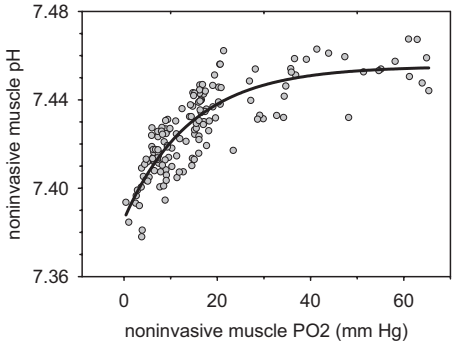

Fig. 13. *Data from one subject, including post-LBNP hyperemia. Noninvasive muscle pH, representing oxygen consumption, as a function of noninvasive muscle PO_2, representing oxygen delivery. Line shows data fit to the equation $pH = B_1 + B_2(1 - e^{-po_2/PO2crit})$. Figure provided courtesy of Dr. Babs Soller.*

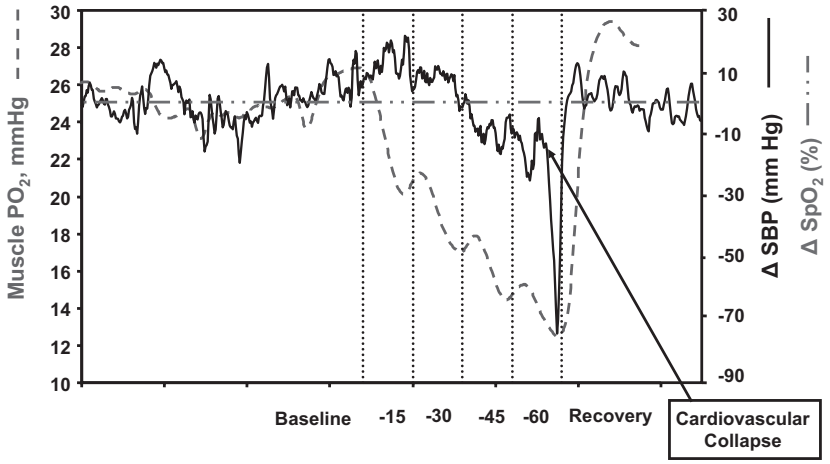

Fig. 12. *Change in systolic blood pressure (ΔSBP, solid line), arterial oxygen saturation (ΔSpO_2, broken dots/dashes line), and muscle oxygen (PO_2, broken line) to progressive central hypovolemia induced by LBNP in a single subject.*

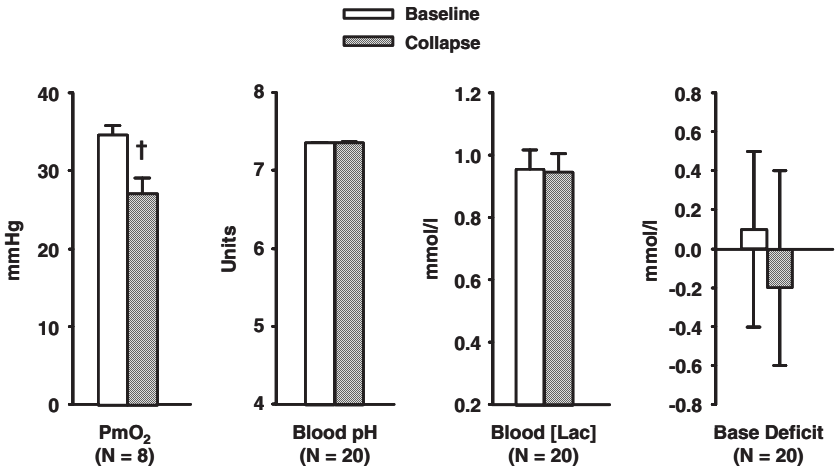

Fig. 14. *PmO_2, blood pH, blood lactate concentration (Lac_B), and base deficit (BD) are shown for subjects at baseline rest (Baseline) and at the point of cardiovascular collapse (Collapse) as a result of hypovolemic hypotension induced by LBNP. Bars and lines represent mean ± SE values. † denotes* $p < 0.05$ *versus baseline value. PmO_2 data from Soller et al.*[39]

CONCLUSIONS

In a hemorrhaging patient, avoiding circulatory shock and progressive cardiovascular collapse depends on the ability to maintain adequate tissue perfusion in the presence of significant central hypovolemia while LSIs are initiated. Our analyses of data from vital signs and other physiologic measures obtained from trauma patients and healthy human subjects exposed to progressive central hypovolemia provide evidence to support the following conclusions:

1. Because of autonomically-mediated compensatory mechanisms, standard vital signs can remain unchanged or change too late when cardiovascular collapse is imminent. As a result, currently proposed closed-loop resuscitation and oxygen delivery systems controlled by arterial blood pressure and SpO_2[21,22,41] might benefit by the inclusion of the metrics presented in this paper.
2. In addition to standard vital signs, there is compelling evidence that continuous capture of PP, ECG R-wave amplitude, metrics of heart period variability, cardiac BRS, and/or muscle PO_2 could improve the sensitivity of closed-loop resuscitation and oxygen delivery by providing earlier indications of clinical status.
3. Before integration into closed-loop control of ventilation, oxygenation, and fluid resuscitation that are currently undergoing testing in the clinical arena,[21,22,41] the application of new physiologic measures as presented in this review will require rigorous clinical testing to determine whether they provide improved feedback control over currently monitored vital signs.

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